Sympathetic activity, assessed by power spectral analysis of heart rate variability, in white-coat, masked and sustained hypertension versus true normotension

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Objective To assess, in a population-based approach, sympathetic nervous system activity by the use of power spectral analysis of heart rate variability, in normotension, white-coat hypertension, masked hypertension and sustained hypertension.

Methods The electrocardiographic RR interval was registered in the supine and standing positions and the low-frequency and high-frequency components of its variability were quantified. Cut-off values of 140/90 mmHg for conventional blood pressure and 135/85 mmHg for daytime ambulatory blood pressure were used to define the four blood pressure groups.

Results After exclusion of patients with diabetes, myocardial infarction or treated hypertension, 1485 subjects with complete data remained for the analysis in the supine position. Age averaged 39 ± 14 years; 54% were women. Conventional and ambulatory blood pressure averaged, respectively, 122 ± 16/79 ± 11 mmHg and 124 ± 12/77 ± 8 mmHg. After adjusting for demographic, anthropometric and lifestyle characteristics, the low-frequency to high-frequency ratio (geometric mean) averaged 0.81 in normotension and was significantly higher in white-coat hypertension (1.11; $P<0.001$), based on a higher low-frequency component and a lower high-frequency component ($P<0.01$). This ratio was not significantly different between normotension, masked hypertension (0.97) and sustained hypertension (0.93). The adjusted standing-to-supine ratio of the high-frequency component (geometric mean) was significantly higher in sustained hypertension (0.50) than in normotension (0.39; $P<0.01$), but not in white-coat (0.40) and masked hypertension (0.45).

Conclusion The findings at rest are compatible with increased sympathetic activity and decreased parasympathetic modulation in white-coat hypertension, with normal autonomic cardiac regulation in masked and sustained hypertension. In addition, sustained hypertension is characterized by a blunted decrease of the high-frequency component on standing. *J Hypertens* 25:2280–2285 © 2007 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Measurements of plasma catecholamines and norepinephrine spill-over, data from direct recordings from peripheral nerves and from power spectral analysis (PSA) of heart rate variability (HRV), and responses to pharmacological blockade suggest that the autonomic nervous system contributes to the development and maintenance of high blood pressure in human essential hypertension, or at least in subsets of patients. These investigations pointed to stimulation of the sympathetic nervous system (SNS) or a decrease in parasympathetic activity [1–5]. Data on the activity of the SNS have not, however, always been consistent [6]. In addition, the definition of normotension and hypertension has usually been based on clinic blood pressure measurements in these studies, without considering out-of-office blood pressure. When both clinic and out-of-office blood pressure measurements are taken into account, four blood pressure categories can be identified: true normotension, white-coat hypertension (WCHT), masked hypertension (MHT) and sustained hypertension (SHT). Therefore, hypertensive and normotensive controls may, respectively, have included patients with WCHT or MHT. Several more recent studies have reported on WCHT separately, and found that SNS activity is deranged in WCHT [7–10], or that the white-coat effect is significantly related to mental stress [11]. No data are, however, available on MHT. Furthermore, it has been suggested that sympathetic tone tends to decrease in later phases of hypertension [4,6,9]. Another possible concern is that most studies on the role of the SNS have been performed on selected hypertensive patients and controls, which may have influenced the results. The purpose of this population-based study was to assess heart rate and the spectral components of its variability as indices of SNS activity in the different types of hypertension. PSA of short-term beat-to-beat HRV, which is largely dependent on the functioning of the autonomic nervous system, provides a non-invasive method to assess autonomic cardiac modulation, suitable for studies in the population.

Methods

Study population

The study population was recruited in eight centres in Europe, that is one centre in Belgium, Bulgaria, Italy, Poland, Romania and the Russian Federation, and two centres in the Czech Republic. The study was part of the EPOGH project (European Project on Genes in Hypertension) and was coordinated by the Hypertension Unit of the University of Leuven K.U. Leuven. The sampling unit consisted of randomly recruited households in a Flemish rural area in Belgium [5,12] and of nuclear families in the other centres [13]. The study was approved by the ethics committee of each centre and the subjects gave informed consent.

Study protocol

Investigations were performed throughout the day in local examination centres, as described, mostly on week days [5,12,13]. Subjects refrained from smoking, heavy exercise, and drinking alcohol or caffeine-containing beverages for at least 2 h before the examinations. They completed a questionnaire on medical history, smoking habits, consumption of alcohol, occupational and leisure-time physical activity, and use of medication. After measurements of height and weight, conventional blood pressure was taken five times by use of the auscultatory technique (Korotkoff phases 1 and 5) by trained investigators, after 5 min of rest in the sitting position; the five measurements were averaged for the analyses. A suitable lead was then selected from the 12-lead electrocardiogram (ECG) for the study of HRV. After the subjects had rested for 20 min in the supine position, the ECG signal was recorded during 15 min in the supine position and 15 min in the free-standing position, together with the signal from a nasal thermistor to assess respiratory frequency.

The analysis of heart rate, HRV and the analysis of respiratory activity has previously been described in detail [12,13]. Analyses were performed in segments of 512 consecutive beats unless only shorter periods were suitable for analysis. The mean RR interval (ms) and its total power (ms^2) and partial power (power between 0.03 and 0.50 Hz; ms^2) were calculated. PSA was then performed by fast Fourier transform to estimate the powers in the low-frequency and high-frequency ranges. The low and high-frequency components included the power from 0.05 to 0.15 Hz and from 0.15 to 0.50 Hz, respectively [14], and were expressed in normalized units (absolute units divided by partial power; %). In addition, the low-frequency : high-frequency power content ratio was calculated. We have previously shown that there were no significant differences between measurements in the morning and in late afternoon [15].

Ambulatory blood pressure (ABP) monitoring was performed with validated devices. The recorders were programmed to obtain measurements at an interval of 15–20 min from 0800 until 2200 h and every 30–45 min for the remainder of the time. Results are from unedited recordings. We calculated the average daytime ABP from 1000 to 2000 h [16] and the average 24-h ABP, weighted by the time interval between successive readings. In the primary analysis, subjects with normal conventional blood pressure (< 140/90 mmHg) and normal daytime ABP (< 135/85 mmHg) were classified as true normotensives. White-coat hypertensives had isolated conventional blood pressure elevation, masked hypertensives isolated ambulatory hypertension, and both blood pressures were elevated in subjects with SHT. In a secondary analysis, we used the average 24-h ABP for the classification of the subjects in the four categories, with cut-off values of 130 mmHg for systolic blood pressure and 80 mmHg for diastolic blood pressure.

Statistical analysis

Database management and statistical analyses were performed using SAS software version 8.2 (SAS Institute Inc., Cary, North Carolina, USA). Values are reported as means and standard deviation (SD) or as proportions. Variables with positively skewed distribution were normalized by logarithmic transformation and are reported as geometric means (antilog of mean log). Statistical analyses were performed by the use of the Student's *t*-test, analysis of variance, analysis of covariance and regression analysis. We adjusted for age, sex, body mass index (BMI), smoking (coded 1 for current smokers and 0 for non-smokers), alcohol consumption (coded 1 for drinkers and 0 for teetotalers), physical activity during leisure time (sports and walking) and at work, expressed in energy expenditure (kcal), and centre (seven design variables). Adjustment for multigroup comparisons was performed by Scheffé's test. We also assessed whether there were significant interactions between blood pressure group and centre, and performed sensitivity analyses with the consecutive exclusion of each centre from the analyses. Orthostatic changes are expressed as standing-to-supine ratios. A two-tailed P value of 0.05 or less was considered significant.

Table 1 Characteristics of the study population by blood pressure group

	Normotension	WCHT	MHT	SHT	Overall P value
Number	1020	146	176	143	
Age (years)	36.1 ± 13.5	49.5 ± 13.8[a]	39.9 ± 14.1[a,b]	47.7 ± 12.0[a,c]	< 0.001
Sex (% women)	61.5	43.2[a]	36.4[a]	32.9[a]	< 0.001
Body mass index (kg/m^2)	23.9 ± 4.2	27.1 ± 4.6[a]	25.4 ± 3.8[a,b]	27.5 ± 4.3[a,c]	< 0.001
Smokers (%)	29.1	17.8[a]	38.1[b]	33.6[b]	< 0.001
Alcohol users (%)	27.6	29.5	45.5[a,b]	51.7[a,b]	< 0.001
Energy expenditure (kcal/day)	1664 ± 930	1674 ± 1288	1810 ± 956	1542 ± 919	0.11
Blood pressure (mmHg)					
Clinic					
Systolic	115.6 ± 10.7	141.8 ± 14.9[a]	123.4 ± 9.2[a,b]	148.8 ± 15.6[a,b,c]	< 0.001
Diastolic	74.9 ± 7.9	92.2 ± 6.1[a]	79.3 ± 7.3[a,b]	95.6 ± 10.3[a,b,c]	< 0.001
Daytime					
Systolic	119.2 ± 8.0	124.8 ± 7.0[a]	136.3 ± 7.3[a,b]	142.7 ± 11.5[a,b,c]	< 0.001
Diastolic	73.8 ± 5.4	77.8 ± 5.3[a]	85.6 ± 6.2[a,b]	90.3 ± 7.8[a,b,c]	< 0.001

MHT, Masked hypertension; SHT, sustained hypertension; WCHT, white-coat hypertension. Values are means ± SD or proportions. Significant differences between groups according to Scheffé's test ($P \leq 0.05$): comparison with, respectively, [a]normotension, [b]WCHT and [c]MHT.

Results

A total of 2490 subjects were investigated in the local examination centres. The response rate of invited subjects in the various centres ranged from 54 to 82% (weighted mean 64%). For the current analyses we excluded participants with at least one of the following conditions: age less than 18 years ($n = 25$); diabetes ($n = 96$); history of myocardial infarction ($n = 16$); antihypertensive treatment ($n = 415$); missing demographic or anthropometric data ($n = 108$); missing or inadequate data with regard to conventional blood pressure ($n = 97$) or ABP measurements ($n = 263$), or with regard to recordings for the analysis of HRV in the supine position ($n = 322$). A total of 1485 of the 2490 subjects had none of these conditions and remained for the analyses. Their age averaged 39.0 ± 14.3 years and BMI averaged 24.8 ± 4.4 kg/m^2; 53.9% were women, 29.5% smoked and 32.2% used alcohol. Conventional blood pressure averaged 122.3 ± 16.4/79.1 ± 10.9 mmHg and daytime ABP averaged 124.0 ± 11.6/77.2 ± 8.1 mmHg. mmHg. The contribution of the different countries was as follows: Belgium, 30.1%; Russian Federation, 15.5%; Poland, 15.3%; Czech Republic, 13.3%; Italy, 12.7%; Romania, 8.3%; and Bulgaria, 4.8%. A total of 1379 of the 1485 subjects had adequate recordings for the analysis of HRV in the standing position.

Table 1 summarizes the major characteristics of the subjects according to blood pressure group. Of the 1485 subjects, 68.7% were normotensive and, respectively, 9.8, 11.9 and 9.6% had WCHT, MHT and SHT. The groups differed significantly with regard to age, sex, BMI, and lifestyle characteristics, but not for energy expenditure (Table 1).

The difference between conventional blood pressure and daytime ABP averaged −1.7 ± 13.7 mmHg for systolic blood pressure and +1.9 ± 9.4 mmHg for diastolic blood pressure in the total study population. Table 2 gives the results from multivariable regression analysis on the determinants of the white-coat effect; blood pressure was included in this analysis as the average of conventional blood pressure and daytime ABP. The difference between conventional blood pressure and daytime ABP became larger with increasing blood pressure and age, and was smaller in smokers and drinkers, with no effect of energy expenditure. The reverse holds for the difference between daytime ABP and conventional blood pressure.

Table 3 summarizes the overall results on heart rate, HRV and breathing frequency in the supine and standing positions. Heart rate, the low-frequency component of its variability, the low-frequency : high-frequency ratio and breathing frequency were higher in the standing than in the supine position, whereas total and partial power and the high-frequency component were lower. The standing-to-supine ratio averaged 1.27 for heart rate, 1.53 and 0.41 for the low and high-frequency components, respectively, and 3.71 for the low-frequency : high-frequency ratio (geometric mean for the latter three variables; $P < 0.001$ for all).

Table 4 summarizes the relationships of conventional blood pressure and daytime ABP, and of their difference, with heart rate and the components of its variability.

Table 2 Determinants of the difference between conventional blood pressure and daytime ambulatory pressure: results from multivariable regression analysis

	CBP – Daytime ABP	
	Systolic	Diastolic
Blood pressure (mmHg)[a]	+0.345[‡]	+0.244[‡]
Age (years)	+0.275[‡]	+0.073[‡]
Sex (women, 1; men, 0)	+1.74[†]	−2.04[‡]
Body mass index (kg/m^2)	NS	+0.322[‡]
Smoking (yes, 1; no, 0)	−2.04[†]	−1.37[†]
Use of alcohol (yes, 1; no, 0)	−1.51*	−1.20*
Energy expenditure (kcal/day)	NS	NS
Intercept	−56.4[‡]	+24.1[‡]
R^2	0.25	0.16

ABP, Ambulatory blood pressure; CBP, conventional blood pressure. Data are regression coefficients. The regression models for the difference between daytime ambulatory blood pressure and conventional blood pressure as the dependent variable are obtained by changing the sign of the regression coefficients. [a]Blood pressure is the average of conventional blood pressure and daytime ambulatory blood pressure. *$P \leq 0.05$; [†]$P \leq 0.01$; [‡]$P \leq 0.001$.

Table 3 Heart rate and heart rate variability in the supine and standing position

	Supine	Standing
Number	1485	1379
RR-interval (ms)	923 ± 135	736 ± 111
Heart rate (min^{-1})	66.4 ± 9.7	83.4 ± 12.5
Total power (log ms^2) (geometric mean)	3.27 ± 0.43 (1851)	3.07 ± 0.41 (1182)
Partial power (log ms^2) (geometric mean)	3.06 ± 0.49 (1143)	2.82 ± 0.45 (666)
LF component (%)	39.6 ± 15.6	58.3 ± 16.9
HF component (%)	46.0 ± 19.0	21.4 ± 14.4
LF : HF ratio (log) (geometric mean)	−0.061 ± 0.393 (0.87)	0.508 ± 0.416 (3.22)
Breathing frequency (min^{-1})	15.8 ± 3.2	16.1 ± 3.4

HF, High-frequency; LF, low-frequency. Values are means ± SD. $P < 0.001$ for changes from supine to standing position in the 1379 subjects with data in both positions.

Systolic and diastolic conventional blood pressure and daytime ABP were positively and independently related to heart rate and the low-frequency : high-frequency ratio and negatively to the high-frequency component; in addition, diastolic blood pressure was positively related to the low-frequency component. It is of note that the relationships were similar for conventional blood pressure and daytime ABP, and that the difference between conventional blood pressure and daytime ABP was not related to the HRV components.

Table 5 summarizes the results on HRV in the four groups of subjects in the supine position, with adjustment for centre and demographic, anthropometric and lifestyle characteristics. Subjects with WCHT had a higher low-frequency component ($P < 0.01$) and low-frequency : high-frequency ratio ($P < 0.001$) and a lower high-frequency component ($P < 0.001$) than normotensive individuals. The components of HRV were not significantly different between MHT, SHT and normotension. Heart rate was slightly higher in SHT than in normotension ($P < 0.05$). Among the demographic, anthropometric and lifestyle characteristics, age, sex and smoking were significantly and independently related to the components of HRV ($P < 0.001$ for all). For example, the low-frequency : high-frequency ratio increased with aging, was lower in women than in men, and was lower in smokers than in non-smokers. The analyses on the inter-group comparisons of the components of HRV and the low-frequency : high-frequency ratio were repeated with the consecutive exclusion of each centre. In each of these analyses the results were similar to the overall results. In addition, the interaction term between blood pressure group and centre was never significant. Finally, results on the inter-group comparisons of HRV were similar when the average 24-h ABP rather than daytime ABP was used for the classification of the subjects in the four blood pressure categories.

Table 6 gives the adjusted results for the standing-to-supine ratio for the four groups of subjects. The response to standing was not significantly different between WCHT, MHT and normotension. SHT showed a lesser decrease in the high-frequency component on standing ($P < 0.01$) with a smaller increase in the low-frequency : high-frequency ratio ($P = 0.07$). The standing-to-supine ratio of heart rate tended to be lower in SHT (1.24) than in normotension (1.27; $P = 0.08$).

Discussion

Normotension and hypertension have classically been defined on the basis of a normal or elevated conventional blood pressure, but it has been recognized that out-of-office blood pressure may be elevated in subjects with normal conventional blood pressure (MHT), or may be normal in subjects with high conventional blood pressure (WCHT). In the current population-based study, WCHT, MHT and SHT were present in, respectively, 68.7, 9.8, 11.9 and 9.6% of the participants. It is, however, likely that the prevalence of WCHT and SHT was underestimated because we excluded subjects treated with antihypertensive drugs, and subjects with high conventional blood pressure are more likely to be treated than others. The true prevalence of the different forms of hypertension is not known in our study population because conventional blood pressure and ABP before the initiation of antihypertensive treatment are not available. Nevertheless, the data shed some light on the general characteristics of the different types of hypertension. There were more men than women in the three hypertension groups than in normotension. Age and BMI were higher in hypertensive individuals, the differences with normotension being smallest for MHT. The prevalence

Table 4 Relationships of conventional blood pressure and daytime ambulatory blood pressure and their difference, with heart rate and the components of heart rate variability

	CBP	Daytime ABP	CBP − ABP
Systolic blood pressure (mmHg)			
Heart rate (min^{-1})	+0.196 ± 0.03795‡	+0.0699 ± 0.0290*	+0.126 ± 0.0334‡
LF (%)	+0.0406 ± 0.0236	+0.0280 ± 0.0179	+0.0125 ± 0.0207
HF (%)	−0.0544 ± 0.0203†	−0.0386 ± 0.0154†	−0.0158 ± 0.0178
LF : HF (log)	+2.247 ± 0.958*	+1.734 ± 0.728*	+0.512 ± 0.841
Diastolic blood pressure (mmHg)			
Heart rate (min^{-1})	+0.130 ± 0.0253‡	+0.085 ± 0.0213‡	+0.043 ± 0.0241
LF (%)	+0.0566 ± 0.0157‡	+0.0609 ± 0.0131‡	−0.00431 ± 0.0149
HF (%)	−0.0553 ± 0.0135‡	−0.0535 ± 0.0113‡	−0.00171 ± 0.0128
LF : HF (log)	+2.555 ± 0.638‡	+2.699 ± 0.532‡	−0.144 ± 0.606

HF, High-frequency; LF, low-frequency. Data are regression coefficients ± SE, with adjustment for age, sex, body mass index, energy expenditure, smoking, alcohol use and centre. $^{*}P \leq 0.05$; $^{†}P \leq 0.01$; $^{‡}P \leq 0.001$.

Table 5 Heart rate and heart rate variability in the supine position by blood pressure group

	Normotension	WCHT	MHT	SHT	Overall P value
Number	1020	146	176	143	
Heart rate (min^{-1})	65.9 ± 9.5	67.4 ± 9.7	66.7 ± 9.4	$68.7 \pm 9.7^{*}$	< 0.01
Total power (log ms^2) (geometric mean)	3.27 ± 0.38 (1874)	3.28 ± 0.39 (1886)	3.30 ± 0.38 (1985)	$3.18 \pm 0.39^{\S}$ (1526)	< 0.05
Partial power (log ms^2) (geometric mean)	3.07 ± 0.41 (1164)	3.05 ± 0.42 (1120)	3.08 ± 0.41 (1212)	2.98 ± 0.42 (955)	0.11
LF component (%)	38.8 ± 15.4	$43.7 \pm 15.7^{\dagger}$	41.3 ± 15.2	39.6 ± 15.6	< 0.01
HF component (%)	47.4 ± 17.9	$40.9 \pm 18.2^{\ddagger}$	44.3 ± 17.7	43.9 ± 18.2	< 0.001
LF : HF ratio (log) (geometric mean)	-0.089 ± 0.378 (0.81)	$0.047 \pm 0.385^{\ddagger}$ (1.11)	-0.012 ± 0.374 (0.97)	-0.030 ± 0.384 (0.93)	< 0.001

HF, High-frequency; LF, low-frequency; MHT, Masked hypertension; SHT, sustained hypertension; WCHT, white-coat hypertension. Values are adjusted means ± SD and geometric means. Values are adjusted for age, sex, body mass index, energy expenditure, smoking, alcohol use and centre. Scheffé's intergroup comparisons according to Scheffé's test: $^{*}P \leq 0.05$; $^{\dagger}P \leq 0.01$; $^{\ddagger}P \leq 0.001$ versus normotension; $^{\S}P = 0.09$ versus normotension and $P = 0.06$ versus MHT; all other comparisons: $P > 0.10$.

of smoking and drinking was highest in MHT and SHT, which may have influenced ABP.

The main purpose of the present study was to assess the activity of the SNS in the three types of hypertension in comparison with true normotension by use of the measurement of HRV in special examination centres. After adjusting for demographic, anthropometric and lifestyle characteristics, several of which differed significantly among the groups, we found evidence of a derangement of the SNS in WCHT, which is a higher low-frequency : high-frequency ratio, resulting from a higher low-frequency component and a lower high-frequency component in comparison with normotension, compatible with increased sympathetic activity and decreased parasympathetic modulation [10]. Involvement of the SNS in WCHT has also been shown by other measurements in the clinic setting, such as microneurography [8,9] and an assessment of plasma norepinephrine [7]. The observation by Pierdomenico *et al.* [17] that the low-frequency : high-frequency ratio is higher in WCHT than in normotension in the period around the clinic visit but not during the rest of the time during 24-h ECG monitoring suggests that the increased low-frequency : high-frequency ratio in WCHT could be the result of an alerting reaction in the clinical setting. The fact that the white-coat effect, used as a continuous variable, was not significantly related to the components of HRV, suggests a more fundamental involvement of the SNS in WCHT.

We are not aware of data on the activity of the SNS in MHT. Heart rate and the components of its variability were no different between MHT and normotension, suggesting that the SNS is not involved in this type of hypertension, at least not when assessed by the use of HRV. It is possible that the elevated ABP is to some extent related to lifestyle factors, as indicated by the higher prevalence of smoking and use of alcohol than in normotension, which is confirmed in the continuous analysis of the determinants of the difference between daytime ABP and conventional blood pressure.

At variance with the results of Neumann *et al.* [10] in selected hypertensive patients, the adjusted values of the low-frequency : high-frequency ratio and of its two components were no different between SHT and normotension. There are three possible explanations for this finding. First, they are consistent with the theory that sympathetic hyperactivity may be involved in the development of essential hypertension, and that in turn this may then modulate sympathetic hyperactivity and induce functional downregulation after prolonged sympathetic stimulation [4,6,9]. For example, Greenwood *et al.* [6] observed by the use of single-unit microneurography that high-normal blood pressure and mild (stage 1) hypertension were characterized by a state of increased central sympathetic drive in comparison with normotensive subjects, but that the greater sympathetic activity was less pronounced in more severe hypertension. Second, because there are separate nerves controlling the heart and blood vessels, the degree of sympathetic stimulation may differ in the heart and in the peripheral vasculature [18]. Functional downregulation of cardiac responses may be paralleled with functional upregulation of vascular responses [19]. This is compatible with the observation by the use of microneurography that muscle sympathetic nerve activity is in general higher in patients with essential hypertension than in normotensive individuals [6,20], and that the elevated

Table 6 Standing-to-supine ratio for heart rate and heart rate variability by blood pressure group

	Normotension	WCHT	MHT	SHT	Overall P value
Number	945	140	164	130	
Heart rate	1.27 ± 0.14	1.26 ± 0.14	1.26 ± 0.14	$1.24 \pm 0.14^{*}$	0.06
Total power	0.947 ± 0.109	0.947 ± 0.111	0.936 ± 0.108	0.960 ± 0.111	0.32
Partial power	0.931 ± 0.127	0.938 ± 0.130	0.923 ± 0.126	0.943 ± 0.129	0.55
LF component (log) (geometric mean)	0.192 ± 0.221 (1.56)	0.164 ± 0.225 (1.46)	0.166 ± 0.218 (1.46)	0.177 ± 0.224 (1.50)	0.33
HF component (log) (geometric mean)	-0.404 ± 0.294 (0.39)	-0.374 ± 0.300 (0.42)	-0.345 ± 0.291 (0.45)	$-0.305 \pm 0.298^{\dagger}$ (0.50)	< 0.01
LF : HF ratio (log) (geometric mean)	0.596 ± 0.445 (3.95)	0.538 ± 0.454 (3.45)	0.511 ± 0.440 (3.24)	$0.482 \pm 0.451^{\ddagger}$ (3.03)	0.01

HF, High-frequency; LF, low-frequency; MHT, Masked hypertension; SHT, sustained hypertension; WCHT, white-coat hypertension. Values are adjusted means ± SD and geometric means. Values are adjusted for age, sex, body mass index, energy expenditure, smoking, alcohol use, and centre. Scheffé's intergroup comparisons according to Scheffé's test: $^{\dagger}P \leq 0.01$ versus normotension; $^{*}P = 0.08$ versus normotension; $^{\ddagger}P = 0.07$ versus normotension; all other comparisons: $P \geq 0.10$.

cardiac norepinephrine spillover in hypertensive patients can be explained, at least partly, by impaired cardiac neuronal norepinephrine reuptake [21]. Third, PSA of HRV does not directly assess central sympathetic discharge, but the response of the cardiac sinus node, so that reduced responsiveness to beta-adrenergic stimulation may also be involved [4].

We also addressed the response of heart rate and HRV to standing and observed impaired reduction of the high-frequency component and a blunted increase of the low-frequency : high-frequency ratio in SHT. This is compatible with another study that indicated a clear impairment of standing-induced changes in spectral autonomic indices in hypertension and even prehypertension [18]. The response to standing was not significantly different between normotension, WCHT and MHT, although a trend towards a progressive impairment was observed.

A number of potential limitations have to be considered. Conventional blood pressure was measured at one visit to the examination centre, and measurements of ABP and HRV have only been performed once, which may have affected the results. As discussed, PSA of HRV assesses only one aspect of SNS activity, that is the response of the cardiac sinus node to the sympathetic and vagal discharge. Data were collected in eight centres throughout Europe, but we found no evidence that the results would differ among the centres.

In conclusion, the findings at rest are compatible with increased sympathetic activity and decreased parasympathetic modulation in WCHT, with normal autonomic cardiac regulation in MHT and SHT. In addition, SHT is characterized by a blunted decrease of the high-frequency component on standing.

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